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Introduction to Zwitterionic Salts

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Zwitterionic salts are hybrid materials, incorporating some characteristics of zwitterions and of ionic liquids, e.g. numerous options for structural design and functionalisation. They comprise of cations and anions in which an additional zwitterionic moiety is embedded into either the cation or the anion. Such materials are characterised by having extended polar domains and high hydrophilicity. Here, we present results from the study of novel zwitterionic salts that are representative examples of this class of materials and illustrate the potential to exploit their functionality and high hydrophilicity.

There is significant interest in generating new highly hydrophilic additives or functional groups that can exceed the performance of doubly-charged zwitterions which are the established benchmark for applications where super-hydrophilicity is required, e.g. for fouling-resistant surfaces.¹⁻³ Short-chain zwitterionic salts (ZWSs) are new materials that contain multiple charge centres in the cationic or the anionic moiety, but only an overall +1 or -1 charge (Fig. 1). It is anticipated that this should lead to strong overall interactions with polar and associative solvents. This will enable novel hydrophilic additives to be prepared that incorporate some of the favourable characteristics of zwitterions and zwitterionic ionic liquids^{4,5} without producing highly charged polyelectrolytes or polyampholytes that are characterised by low solubility. At the same time, ZWSs could preserve advantages of some betaine zwitterions such as effective peptide immobilisation *via* EDS/NHS coupling.⁶ ZWSs (Fig. 1) consist of a cation and an anion, and an additional zwitterionic moiety embedded either in the cation or the anion. Okada and co-workers^{7, 8} and later, Wang *et al.*⁹ have described the surface activity and phase behaviour of some zwitterion-containing sulfonate surfactants. However, the preparation and properties of smaller, non-surfactant salts have not previously been reported. At the moment, the lack of knowledge and experimental data on these materials hinders establishment of guidelines for their design and development of potential applications. Overcoming these limitations is the main goal of this work.

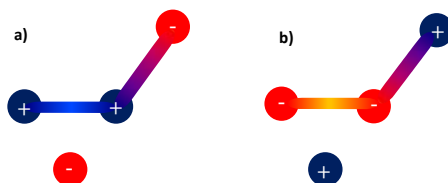
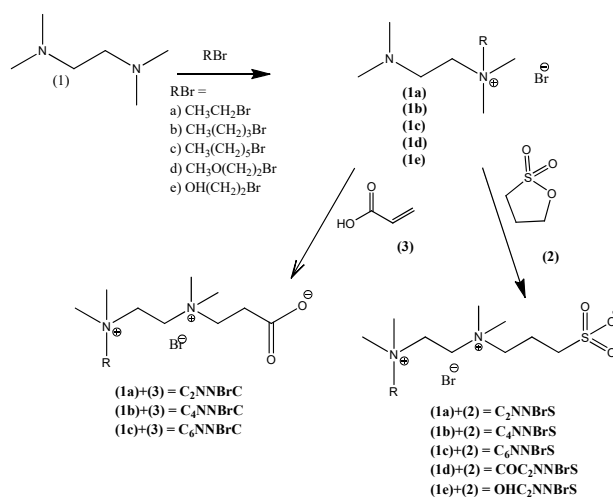


Fig. 1 Pictorial structure of zwitterionic salts with zwitterionic part embedded in a) cation and b) anion.

Herein, we describe a family of representative ZWSs which use ethylene diamine as a core structural motif for cations that include a zwitterionic moiety (Scheme 1). One terminal alkyl ammonium group incorporates ethyl, butyl, hexyl, hydroxyl, or methoxyethyl groups, while the second ammonium group is bound to either a carboxylate or sulfonate group forming a zwitterionic part of the molecule. A series of ZWSs were prepared to test these concepts using a simple two-step synthetic procedure as shown in Scheme 1, to first generate a single cationic site and then to introduce the zwitterionic function. The reactions were all performed with high yields, short reaction times, and under mild reaction conditions (30-40 °C). This makes the materials readily available and simple to modify. Details of the synthesis and characterisation by CHNS analysis, mass spectroscopy, ¹H- and ¹³C-NMR spectroscopy can be found in the ESI.†

All the salts were isolated as solids. The melting points and decomposition temperatures are shown in Table 1. Decomposition temperatures calculated as onset of weight loss in a dynamic thermogravimetric analysis (TGA) scan show that the sulfonate based ZWSs have reasonable thermal stability with decomposition temperatures between 200-230 °C. Similar decomposition temperature ranges have been reported for 1-alkyl-3-methylimidazolium carboxylate ionic liquids.¹⁰ Stability of carboxylate based ZWSs is, however, significantly lower.

Melting points are lower than those for common inorganic salts, but higher than 100 °C. Applying the broad definition of ionic liquids as 'ionic salts which are molten at temperatures below 100 °C',¹¹ these ZWSs cannot be classified as ionic liquids. However, there is a possibility that exchange of bromide anion with a larger, flexible, charge delocalised anion such as bis((trifluoromethyl)sulfonyl)imide would significantly lower the melting point, as already well-documented for ionic liquids.¹¹



Scheme 1. The synthetic scheme

Table 1. Melting points (T_m) and decomposition temperature (T_{dec}) of synthesised ZWSs.

ZWS	$T_m / ^\circ\text{C}$	$T_{dec} / ^\circ\text{C}$
C_2NNBrS	124	242
C_4NNBrS	132	235
C_6NNBrS	- ^a	224
COC_2NNBrS	- ^a	210
OHC_2NNBrS	159	220
C_2NNBrC	115	140
C_4NNBrC	110	- ^b
C_6NNBrC	130	- ^b

^a-compound decomposed without melting, ^b-decomposition event was following the melting and the temperatures could not be clearly distinguished.

Crystals of C_2NNBrS and C_2NNBrC were obtained from solution and were characterised by single crystal diffraction. Details on the crystal preparation and crystallographic characterisation can be found in ESI.† Although crystals were isolated from methanol/acetone solutions, C_2NNBrS crystallised with three water molecules in the asymmetric unit, indicating the high affinity towards water and adsorption ability. The crystal structure of $\text{C}_2\text{NNBrS} \cdot 3\text{H}_2\text{O}$ (Fig. 2a) shows the sulfonate group forming hydrogen bonds with water molecules with an $\text{O} \cdots \text{H}$ distance of 1.872(2) Å; the water molecules also form additional hydrogen bonds with adjacent water molecules ($\text{O} \cdots \text{H}$ distance of 1.935(2) Å). The bromide anions form only weak hydrogen bonding with one of the water molecules in the structure with a $\text{Br} \cdots \text{H}$ distance of 2.4432(2) Å. The water molecules and bromide anions form layers separated by the cations are shown in Fig. S4 ESI†. Similar bridging of zwitterions by water molecules was recently reported by Fucke *et al.*¹² This behaviour is not surprising, knowing that some quaternary ammonium salts also form crystalline hydrates with high proportion of ‘crystal water’.¹³

It should be noticed that the water molecules can be removed from the structure C_2NNBrS by drying the salt under high vacuum (1 Pa) and at a moderate temperature (55 °C) down to 300-500 ppm as measured by coulometric Karl-Fischer titration. However, the removal of water from carboxylate ZWSs under identical condition is not efficient and usually leaves hydrates with 2000-5500 ppm of water.

C_2NNBrC , in contrast to C_2NNBrS , crystallised as a methanol solvate from a methanol/acetone solution, (Fig. 2b) containing a neutral (protonated) carboxylic acid function. There are two bromide anions and two methanol molecules present in the asymmetric unit. The carboxylic acid group of the cation forms weak hydrogen bonds with one of the bromide anions present in the structure with a $\text{Br} \cdots \text{H}$ distance of 2.3888(8) Å. The second bromide anion in the structure forms a weak hydrogen bond with the methanol solvent molecule with an $\text{O} \cdots \text{H}$ distance of 2.4885(9) Å.

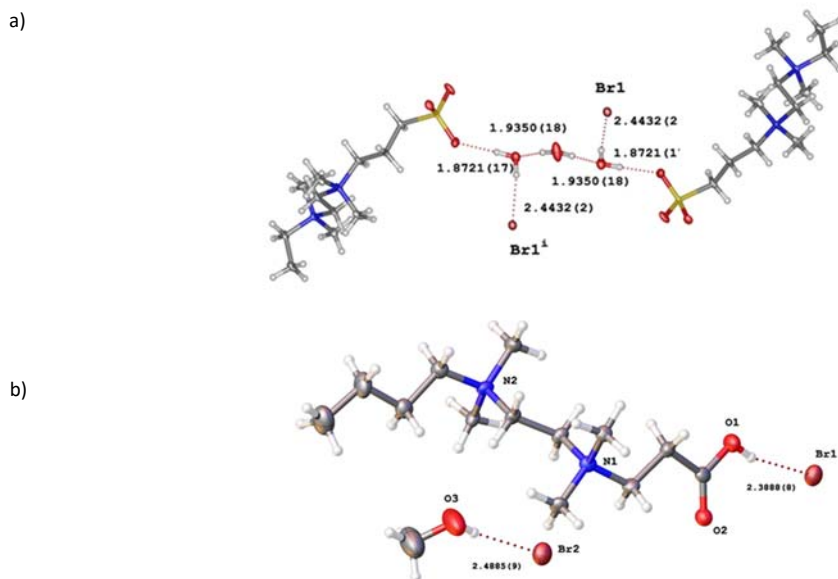


Fig. 2. a) Cation-cation association in crystal of C_2NNBrS and b) C_2NNBrC crystal with a methanol molecule in the structure.

Unlike most ionic liquids, which are usually soluble in many organic solvents such as acetone, acetonitrile, or chloroform, ZWSs have very limited solubility in these solvents. ZWSs exhibit high solubility in water at room temperature approaching 80 wt% (Table 2). For comparison, the solubilities of the simple tetraalkylammonium bromides, $[N(CH_3)_4]Br$ and $[N(C_2H_5)_4]Br$ in water are 51 and 72 wt%, respectively.¹³ Despite their low solubility in organic solvents, we have found that these salts associate *via* hydrogen bond interactions with a range of organic molecules that possess hydrogen bond donor ability forming homogenous mixtures which are liquid at room or close to room temperature.¹⁴ As an additional observation, aqueous ternary mixtures revealed an impressively rich phase behaviour.¹⁴

Table 2. Visually determined solubility of ZWSs in water at 25 °C.

solubility, wt%	C_2NNBrS	C_6NNBrS^a	OHC_2NNBrS^a	C_2NNBrC
	75	74	81	61

^a-Solubility test of C_6NNBrS and OHC_2NNBrS in acetone, acetonitrile, chloroform, toluene, 1,4 dioxane, ethyl acetate and dichloromethane show solubility below the limit of 1H -NMR detection.

Solutions of the ZWSs in water all show solid-liquid equilibria (SLE) points below 0 °C, with a depression of the melting point temperatures as the concentration of ZWS is increased until the concentration of approx. 70 wt% ZWS. The SLE diagram for C_2NNBrS and C_6NNBrS are shown in ESI, Fig. S1†. At concentration higher than 70 wt% of ZWSs, melting points and eutectic compositions could not be determined with accuracy due to the high viscosities of the solutions and steep slope of the temperature-concentration dependence.

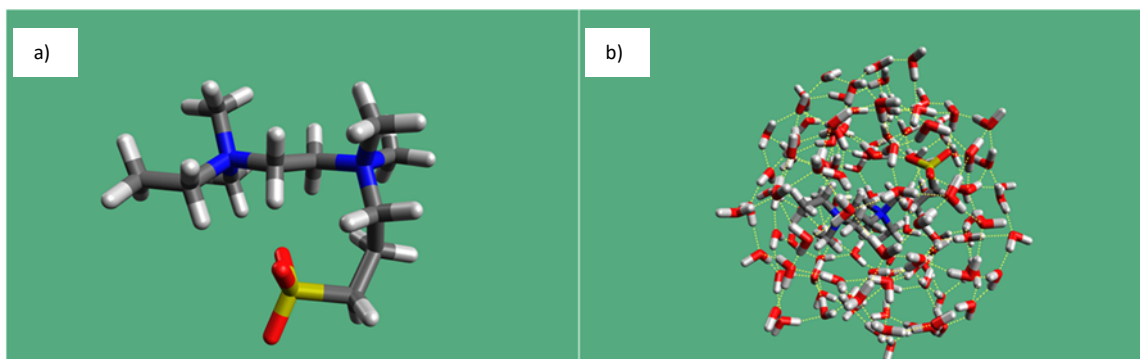


Fig. 3. a) Optimised gas phase geometry of C_2NNS cation, b) 'Quenched' micro-solvation showing that the cation forms hydrogen bonds only with the water molecules.

In order to understand more about the solvation of ZWSs with water, the cation solvation structure was investigated using molecular modelling. The gas phase optimised geometries for isolated ZWS cations (reported in ESI†) show a

tendency to fold in order to minimise their electrostatic energy and form intramolecular hydrogen bonds. The extent of this depends on the molecular geometry. The main points of intramolecular interactions are negatively charged oxygen atoms in sulfonate and acidic protons on methylene groups located between positively charged tetraalkylammonium groups (see the optimised structure of the C₂NNBr cation in Fig. 3a and b). However, when the cation geometry was refined using an implicit model of an aqueous solvent environment, a less compact structure was found. In addition, the intramolecular hydrogen bonds were completely disrupted (Figure S2 ESI[†]). Preliminary numerical result suggests preferential hydrogen-bonded solvation by water in solution supporting observations of high solubility and hydrophilicity.

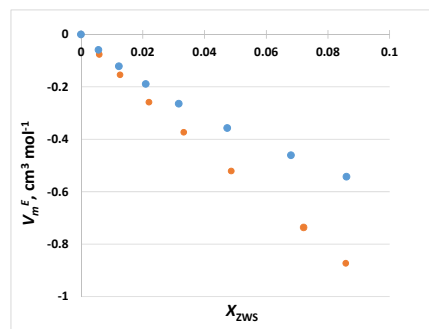


Fig 4. Excess molar volume, V_m^E , as function of molar fraction of ZWS, x_{ZWS} , for (ZWS+ water) binary system at $T=25$ °C; •C₂NNBrS and •OHC₂NNBrS.

Table 3. Excess molar volumes, V_m^E measured at $T=25$ °C and atmospheric pressure, for C₂NNBrS, OHC₂NNBrS, ethylammonium acetate, N₂Ac,¹⁵ n-butylammonium acetate, N₄Ac,¹⁶ and n-butylammonium nitrate N₄NO₃¹⁶.

Salt	C ₂ NNBrS	OHC ₂ NNBrS	N ₂ Ac	N ₄ Ac	N ₄ NO ₃
x_{salt}	0.086	0.086	0.09	0.0992	0.1000
V_m^E	-0.873	-0.543	-0.634	-0.974	-0.398

The acidic protons associated with both alkyl ammonium cationic sites, the negatively charged oxygen atoms in sulphate or carboxylate anionic groups, and the bromide anions should all be available to contribute to strong interactions with water in solution *via* hydrogen bonding. In order to assess the strength of the interactions, excess molar volumes, V_m^E , were calculated from experimental density data for two (ZWS + water) mixtures according to the following equation:

$$V_m^E = \sum_i x_i M_i \left(\frac{1}{\rho} - \frac{1}{\rho_i} \right)$$

where ρ is the density of the solution, and ρ_i and M_i are the density and molecular weight of the pure component i , respectively. The density of C₂NNBrS and OHC₂NNBrS were calculated using group contribution method developed by Padaszyński *et al.*¹⁷ It has been shown that this model predict densities with high accuracy for a broad range of organic salts including dicationic and tricationic ionic liquids.

The magnitude and sign of excess molar volume of a binary mixture can be used as indicators of the strength of interactions between components in a mixture. Negative excess molar volumes were found in dilute aqueous solutions of C₂NNBrS and OHC₂NNBrS. Excess molar volumes in dilute aqueous solutions of C₂NNBrS and OHC₂NNBrS (Fig. 4), and comparable values reported for hydrophilic protic ammonium based ionic liquids are listed in Table 3. The large negative values of V_m^E indicate that there is a significant association between the ZWS and a large number of water molecules, and that this association overcomes positive contribution to the V_m^E coming from the disruption of the water hydrogen-bond network. The association could be caused by formation of hydrogen bonds or improved molecular packing where water molecules fit efficiently into a network of ZWSs molecules in the higher mole fraction ZWS regime. The magnitude of the association is significant, particularly taking into account that this association is competing with the self-association of water molecules and ZWS self-association through ion-ion interactions (Fig. 2a). The excess molar volumes found for the ZWSs in dilute aqueous solution have significantly higher absolute values comparing to methylimidazolium halide ionic liquids¹⁸ and support the hypothesis of Ramjugernath and co-workers¹⁹ that the incorporation of polar and hydrophilic groups into organic cations would result in larger negative excess molar volumes.

Table 4. Vapour pressure of water, p (mbar) for the aqueous mixtures of C_2NNBrS , OHC_2NNBrS , and COC_2NNBrS at given mass fraction (w_{ZWS}) / mole fraction (X_{ZWS}) measured at $T=25$ °C.

ZWS	C_2NNBrS	OHC_2NNBrS	COC_2NNBrS
p / mbar	12	11	14
w_{ZWS}	0.71	0.77	0.72
X_{ZWS}	0.111	0.145	0.109

To further explore the interactions of water with the ZWSs, vapour-liquid equilibria (VLE) were determined in order to assess water activity. Vapour pressure of water for three (ZWS + water) mixtures was determined at 25 °C at ZWS concentrations close to the salt solubility limit at room temperature and the results are shown in Table 4. The values of water vapour pressure show highly non-ideal behaviour with pronounced negative deviations from Raoult's law. This is confirmation of the strong interactions between water and ZWS molecules, and opens up possibilities for the application of ZWS mixtures as a working pair for absorption cycle technology or as entrainers in extractive distillation.

Table 5. Minimum Inhibitory Concentration (μm) of synthesised ZWSs

ZWS	MRSA MIC (μm)	<i>P. aeruginosa</i> PA01 MIC (μm)
C_2NNBrS	>1024	>1024
C_4NNBrS	>1024	>1024
C_6NNBrS	>512	>512

The preliminary toxicity study of ZWSs was carried out by evaluating of their antimicrobial activity. Minimum inhibitory concentrations (MICs) were calculated using standard broth microdilution assays according to NCCLS guidelines²⁰ and as described previously²¹. The test organisms were *Staphylococcus aureus* (methicillin resistant) MRSA ATCC 33593 (Gram positive) and *Pseudomonas aeruginosa* PA01 (Gram negative). The results for minimum inhibitory concentrations of three sulfonate based ZWSs (Table 5) show that the ZWSs were non-toxic to the tested bacteria. It is expected that longer alkyl chain ZWSs would display a moderate antimicrobial activity, similarly to the trend reported in previous studies on alkylated compounds such as 1-alkyl-3-methylimidazolium chlorides²¹.

Conclusions

ZWSs with a complex cation have been investigated as representative examples of this new ionic motif. The materials show strong hydrophilicity characterised by high solubility in water and a strong positive association with water molecules. These characteristics suggest applications in energy, industrial separations and biomedical fields as hydrophilic additives or as functional groups if attached on a polymer backbone. However, in order to further develop these potentially interesting new materials, it is necessary to expand the library with new structures (by systematic variation of the inter-charge chain, the chain length in the zwitterion moiety, type of the anion *etc.*) and evaluate their thermodynamic and transport properties, toxicity profile, and their specific atomistic interactions with water (hydration number, nature of hydrates) and solvent mixtures.

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